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Effectiveness of Cidofovir in Treating Natalizumab-Associated Progressive Multifocal Leukoencephalopathy (PML)

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EFFECTIVENESS OF CIDOFOVIR IN TREATING NATALIZUMAB-ASSOCIATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

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Clinical Question:

Is Cidofovir treatment in Natalizumab-associated Progressive Multifocal Leukoencephalopathy effective in MS Patients?

Background:

Natalizumab (Nz) a monoclonal antibody has been in medicinal use for treatment of Relapsing Remitting Multiple Sclerosis (RRMS) since 2004. Progressive Multifocal Leukoencephalopathy (PML) is one of its serious risks which is a demyelinating disorder of brain associated with John Cunningham Virus (JCV). There have been 801 cases up till December 2018 which were reported with its use[1]. Lack of prospective trials and retrospective studies due to small number of these cases there is no consensus on Nz-associated PML treatment. To date there is no cure for this condition and there is a debate on effectiveness of different modalities[2]. Cidofovir an antiviral drug which is used in cytomegalovirus retinitis, Aciclovir-resistant HSV infections[3, 4]. The antiviral properties of Cidofovir are attributed to its active metabolite Cidofovir diphosphate which inhibits viral replication by impeding viral DNA ploymerases 5. Cidofovir is effective in polyomavirus like BK-virus in kidney transplant recipients. JCV belongs to the same family of Polyomaviruses[5]. Cidofovir has been used in selected cases with PML in various immunosuppressed states, hematological malignancies, post-transplant and HIV for the treatment of PML. This CAT aims to look at the evidence for using Cidofovir in Nz-associated PML.

Search Terms:

Cidofovir, Natalizumab, PML

Search Strategy:

An online search including Pubmed and Cochrane library was conducted dated 12th April 2019 to look for available evidence with search terms as mentioned through below links.
https://www.ncbi.nlm.nih.gov/pubmed/
https://www.cochranelibrary.com

Search Outcome:

Search in Pubmed Central showed 71 studies and case reports with the search term
There were 14 studies and case reports which were studied in depth for this CAT 4 case reports which fulfilled the criteria were included 10 studies which partially encompassed the scope of this CAT were discussed in the references. (Appendix 1)

Search in the Cochrane library with the search terms showed 3 reviews and 120 controlled trials These reviews and controlled trials were beyond the scope of this study, so these were excluded. (Appendix 2)

Evidence Included in This CAT:

1. Pathologic Findings of Chronic PML-IRIS in a Patient with Prolonged PML Survival Following Natalizumab Treatment. Himedan M, Camelo-Piragua S, Mills EA, Gupta A, Aburashed R, Mao-Draayer Y. J Investig Med High Impact Case Rep. 2017 Sep 27;5(3):2324709617734248. doi: 10.1177/2324709617734248. eCollection 2017 Jul-Sep. (Case Report 1 in Table.1)

2. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. N Engl J Med. 2005 Jul 28;353(4):375-81. Epub 2005 Jun 9. (Case Report 3 in Table.1)

3. Progressive multifocal leukoencephalopathy associated to natalizumab extended dosing regimen. Hervás JV, Presas-Rodríguez S, Crespo-Cuevas AM, Canento T, Lozano-Sánchez M, Massuet-Vilamajó A, Ramo-Tello C. Neurodegener Dis Manag. 2015 Oct;5(5):399-402. doi: 10.2217/nmt.15.42. Epub 2015 Oct 30. (Case Report 4 in Table 1)

4. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Clifford DB, DeLuca A, Simpson DM, Arendt G, Giovannoni G, Nath A. The Lancet Neurology. 2010 Apr;9(4):438-46.

Table 1. Cidofovir use in associated Progressive Multifocal Leukoencephalopathy in MS

Reference	C	Condition	Presentation	Diagnosis	DMT's Used	Natalizumab Duration	Drug Regimen	Course	DMT'S Restarted
1.Himedan M et al	49 M	RRMS	Left Arm,Leg, Face weakness and Unsteadiness	MRI Brain, JCV+ PCR in CSF	Interferon beta-1a, Mitoxantrone	3.5 Years	PLEX 5-Days, IVIG IV Methylprednisolone, Cidofovir, Maraviroc, Mirtazepine, Levetiracetam	Seizures, Immune Reconstitution Inflammatory Syndrome (IRIS) 7 weeks after PLEX – Also on Brain Biopsy 3.5 years after death	Interferon beta-1a after 6 months
2. Langer-Gould A et al	44 M	RRMS	Started with a suspicious MRI brain lesion followed by subtle personality changes followed by attention deficits, dysarthria, Left Hemiparesis, cognitive deficits, hemineglect, quadriparesis, and minimal alertness – IRIS developed in brain biopsy 3 months after Natalizumab was stopped	MRI Brain, JCV+ PCR CSF, Brain biopsy	Interferon beta-1a	28 - months	IV Methyl Prednisolone, Cidofovir (5mg/kg) every 2 weeks, IVIG, Cytarabine	After Cidofovir initially the condition deteriorated later cytarabine was added neurological stabilization – pancytopenia ensued given erythropoietin and granulocyte colony-stimulating factor	Not mentioned

3.José Vicente Hervás-García et al	51 M	RRMS	Aphasia was the initial presenting feature with MRI evidence –	MRI Brain consistent with PML, Initially JCV PCR was negativ	No previous DMT's	4 years was on 4 weekly which was chan	PLEX, Cidofovir, Mirtazapine,Mefloquine and IV steroids	In the following 2 months clinical and radiological worsening with 1 months after the diagnosis JCV PCR was +ive which rechecked was	Not mentioned
				e which was positive in 1 month following		ged to 6-weekly for 1 year		-ive at 3 months with improvements Clinically however no specifics given	
4. Clifford DB, DeLuca A, Simpson DM et al	45 F	RRMS	Homonymous hemianopsia	JCV-PCR +ive in CSF	Mitoxantrone, IFN	34 - Months	PLEX, Cidofovir	IRIS Developed at 7 weeks after initiating PML treatment with clinical worsening in cognition	Not Mentioned
5. Clifford DB, DeLuca A, Simpson DM et al	36 F	RRMS	Homonymous hemianopsia, decreased cognition	JCV-PCR +ive, MRI-showed GD-enhancing lesions	Glatiramer acetate, IFN	25-Months	PLEX, mefloquine, mirtazapine, cidofovir	IRIS Developed progression of symptoms	Not mentioned

Summary:

Natalizumab associated PML is one of the major side-effects in Multiple Sclerosis patients. The long-term outcomes vary in individual cases. Patients who develop the condition mainly have two strong associations, the JCV serology titer index and the duration of treatment. In search for answering the question if Cidofovir is effective treatment there is ancillary evidence from case reports supporting it in Natalizumab associated PML. Owing to the small number of these cases a randomized controlled trial encompassing different drugs and including outcome variables is not possible.
An interesting review on PML recommended conflicting evidence on effectiveness of Cidofovir in PML[6]. Studies and reports which suggested ineffectiveness of cidofovir were both conducted in AIDS-associated PML[7-9]. Three interesting non-AIDS related case reports supported Cidofovir with positive outcomes [10-12]. The results of these outcomes in Natalizumab associated PML can they be generalized, remains ambiguous.
In a case series of 28 Natalizumab associated patients 2 of the patients received Cidofovir their treatment outcomes at 3-months showed stabilization [13]. Adjunctive therapy including plasma exchange, and Cidofovir in one patient was used. The second patient was treated with Cidofovir, Mirtazepine, Mefloquine and Plasma Exchange[13].
In this CAT an analysis of 5 cases were included of Natalizumab associated PML which were treated with Cidofovir in different treatment combinations. Owing to small number of cases which encompassed this CAT it is difficult to come to any specific conclusion. There was clinical stabilization in 4 cases that was achieved, and 1 case had an initial deterioration. In all the 5 cases there was a serological remission at the end. One strong reason for such an observation could be a publication bias. Multi-drug regimen specific to each case was used including Mirtazepine, Mefloquine, Cidofovir, Cytarabine, and plasma exchange. These are further individually classified in Table.1.

Clinical Bottom Line:

It's very difficult to generalize the results of this CAT due to the small number of cases which are associated with Natalizumab treated with Cidofovir and an unavailability of Randomized controlled trials.
However, the results which did encompass a small number of patients were suggestive of serological remission, and clinical stabilization with Cidofovir and the adjunctive therapy.

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